METHODS OF TREATING AN AUTOIMMUNE DISEASE

CROSS REFERENCE TO PRIOR APPLICATIONS

[0001] This application claims priority under the Paris Convention to U.S. Provisional Patent Application 62/724,714, filed Aug. 30, 2018, and U.S. Provisional Patent Application 62/770,408, filed Nov. 21, 2018, each of which are incorporated herein by reference as if set forth in their entirety.

FIELD OF THE DISCLOSURE

[0002] The present disclosure relates generally to the field of immunology. More particularly, the present disclosure relates to methods of treating an autoimmune disease.

BACKGROUND OF THE DISCLOSURE

[0003] After initial encounter with antigen, B cells can differentiate into plasmablasts (PB), plasma cells (PC) and memory B cells. PB, which are rapidly produced upon antigen encounter, are short-lived effector cells whereas PC are long-lived mediators of lasting humoral immunity (Koch et al., 1981; Nutt et al., 2015). In humans, long-lived PC that have downregulated B220 and CD19 lineage markers produce specific antibodies (Ab) for years after encountering their cognate antigens (Manz et al., 1998).

[0004] Studies in mice indicate that long-lived PC reside in the bone marrow (BM) in niches that are rich in survival factors such as Interleukin-6 (IL-6), B-cell Activating Factor (BAFF) and A Proliferation Inducing Ligand (APRIL) (Chu and Berek, 2013). Analogous cytokine-rich niches exist in the gut lamina propria supporting mucosal IgA^{+} PC (Chu et al., 2014).

[0005] PC have been associated with disease pathogenesis, including autoimmune diseases such as Multiple Sclerosis (MS) where they have been found both in the central nervous system (CNS) parenchyma, cerebral spinal fluid (Ritchie et al., 2004) and in the meninges (Serafini et al., 2004). Treatment of relapsing-remitting MS (RRMS) with anti-CD20 antibodies that deplete B cells is followed by rapid and durable suppression of relapses, and prevention of newly formed inflammatory lesions in the CNS (Hauser et al., 2008; Kappos et al., 2011).

[0006] However, this therapy does not target $CD20^{neg}$ PC. Accordingly, oligoclonal immunoglobulin bands in the cerebrospinal fluid (CSF) of MS patients, a diagnostic hallmark of the disease, are unchanged following anti-CD20 treatment (Piccio et al., 2010). In contrast to anti-CD20 therapy, treatment with atacicept (TACI-Ig), an agent that neutralizes both APRIL and BAFF, not only reduces circulating B cells but also decreases serum Ab titres, particularly IgM and IgA (Tak et al., 2008). Atacicept was tested in RRMS with the sensible hypothesis that depletion of a broader array of B lineage cells would have an even more beneficial effect on the disease than anti-CD20 therapy. Surprisingly however, treatment of RRMS patients with atacicept resulted in dose-dependent disease exacerbations (Kappos et al., 2014), and also promoted the development of MS in optic neuritis patients (Sergott et al., 2015).

[0007] There is a need to better understand how B cells regulate autoimmune diseases. There is also a need for improved methods of treating autoimmune diseases, such as MS.

SUMMARY OF THE DISCLOSURE

[0008] The inventors have invented methods of treating an autoimmune disease in a subject.

[0009] In an aspect of the disclosure, a method of treating an autoimmune disease in a subject is provided. The method comprises administering an effective amount of one or more of:

[0010] a B-cell Activating Factor (BAFF) polypeptide;

[0011] a BAFF polypeptide and an agent that promotes survival and/or migration of gut-derived commensal-reactive B cells to the central nervous system of the subject;

[0012] a BAFF polypeptide and an agent that depletes B cells; or

[0013] a BAFF polypeptide and a gut commensal that increases IgA levels to the subject.

[0014] In an embodiment of the method of treating an autoimmune disease in a subject provided herein, the autoimmune disease is a non-systemic organ-specific autoimmune disease.

[0015] In an embodiment of the method of treating an autoimmune disease in a subject provided herein, the autoimmune disease is multiple sclerosis.

[0016] In an embodiment of the method of treating an autoimmune disease in a subject provided herein, the BAFF polypeptide is fused to the human Fc region of an immunoglobulin polypeptide.

[0017] In an embodiment of the method of treating an autoimmune disease in a subject provided herein, the commensal-reactive B cells are IgA+ plasmablasts and/or plasma cells.

[0018] In an embodiment of the method of treating an autoimmune disease in a subject provided herein, the commensal-reactive B cells express interleukin-10 (IL-10) and/or inducible nitric oxide synthase (iNOS).

[0019] In an embodiment of the method of treating an autoimmune disease in a subject provided herein, the agent that promotes survival and/or migration of gut-derived commensal-reactive B cells is a cytokine or a chemokine.

[0020] In an embodiment of the method of treating an autoimmune disease in a subject provided herein, the agent that promotes survival and/or migration of gut-derived commensal-reactive B cells is IL-10 and/or iNOS.

[0021] In an embodiment of the method of treating an autoimmune disease in a subject provided herein, the agent that depletes B cells comprises an antibody.

[0022] In an embodiment of the method of treating an autoimmune disease in a subject provided herein, the agent that depletes B cells comprises an antibody that binds to CD19 and/or CD20.

[0023] In an embodiment of the method of treating an autoimmune disease in a subject provided herein, the gut commensal is a commensal microbe.

[0024] In an embodiment of the method of treating an autoimmune disease in a subject provided herein, the administering an effective amount of a gut commensal comprises oral or rectal administration of a microbe or community of microbes.

[0025] In an embodiment of the method of treating an autoimmune disease in a subject provided herein, the gut